PATENT COOPERATION TREATY

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REC'D 23 AUG 2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SJB/PB60320	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2004/006592	International filing date *(day/month/year)* 17.06.2004	Priority date *(day/month/year)* 19.06.2003
International Patent Classification (IPC) or national classification and IPC A61K31/4025, C07D409/12, C07D409/14, C07D413/14, A61P7/02		
Applicant GLAXO GROUP LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.11.2004	19.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Cortés, J Telephone No. +49 89 2399-8206

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006592

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-40	as originally filed

Claims, Numbers

1, 2(part)	as originally filed
2(part), 3-12	received on 25.11.2004 with letter of 25.11.2004

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11

because:

☒ the said international application, or the said claims Nos. 11 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(Indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006592

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10,12
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

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Re Item I

Basis of the opinion

With letter of 25.11.2004 the Applicant has filed a new claim 4. The other claims have been renumbered accordingly. The basis for this claim can be found on page 7 of the description.

These amendments are in line with 70.2(c) PCT, since they do not extent beyond the content of the application as originally filed.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 11 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion with regard to the industrial applicability will be formulated for this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following document has been cited in the International Search Report:

D1: WO 03/043981 A (GLAXO (GB)) 30 May 2003 (2003-05-30)

Novelty (Article 33(2) PCT)

The present compounds differ from the compounds in D1 in the groups X and R2.

Inventive Step (Article 33(3) PCT)

D1 discloses factor Xa inhibitors and can be regarded as the closest prior art.

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The problem of the invention was the provision of new factor Xa inhibitors.

D1 does not suggest the subtitution of the pyrrolidons disclosed therein with a phenyl or a heterocyclic group in position 1.

The present invention is therefore based on an inventive step.

Re Item VI
Certain documents cited

The following P-document has been cited in the International Search Report:

D2: WO 03/053925 A (GLAXO (GB)) 3 July 2003 (2003-07-03)

The priority documents pertaining to the present application were not available at the time of establishing this report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the P-document D2 cited in the international search report could become relevant to asses whether the present claims satisfy the criteria set forth in Article 33(1) PCT.

It is noted that there is no generic overlap with D2 due to the proviso for R2 (exclusion C2-3alkyl-morpholino) and the definition of Rf in R2=C1-3alkylRf (Rf can not be morpholino).

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each ring of which optionally contains a further heteroatom N,
Z represents an optional substituent halogen,
alk represents alkylene or alkenylene,
T represents S, O or NH,
and/or pharmaceutically acceptable derivative thereof.

3. A compound according to claim 1 or claim 2 wherein R^2 represents -C_{1-6}alkyl, -C_{0-3}alkylR^c, C_{1-3}alkylR^f, -C_{2-3}alkylNR^aR^b, -C_{2-3}alkylOC_{1-6}alkyl, -C_{2-3}alkylOC_{1-3}alkyl$CONR^aR^b$ and/or pharmaceutically acceptable derivative thereof.

4. A compound according to claim 1 or claim 2 wherein R^2 represents –C_{0-3}alkylR^c, -C_{1-3}alkylR^f, -C_{2-3}alkylOC_{1-6}alkyl, -C_{2-3}alkylOC_{1-3}alkyl$CONR^aR^b$ and/or pharmaceutically acceptable derivative thereof.

5. A compound according to any one of claims 1-4 wherein X represents phenyl or a 5 or 6 membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: halogen, -C_{1-4}alkyl or -NR^aR^b.

6. A compound according to any one of claims 1-5 wherein Y represents a substituent selected from -$C(O)NR^aR^b$, -$S(O)_nR^d$, -$S(O)_2NR^aR^b$, -$N(C_{1-4}alkyl)(CHO)$ or -$NHSO_2R^d$ and/or pharmaceutically acceptable derivative thereof.

7. A compound according to claim 1 selected from:
4-{(3*S*)-3-[{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}(cyclopropylmethyl)amino]-2-oxo-1-pyrrolidinyl}-3-fluoro-*N*,*N*-dimethylbenzamide;
4-((3*S*)-3-{{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}[3-(dimethylamino)propyl]amino}-2-oxo-1-pyrrolidinyl)-3-fluoro-*N*,*N*-dimethylbenzamide;
4-((3*S*)-3-{{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}[2-(dimethylamino)ethyl]amino}-2-oxo-1-pyrrolidinyl)-3-fluoro-*N*,*N*-dimethylbenzamide;
4-[(3*S*)-3-({2-[(2-Amino-2-oxoethyl)oxy]ethyl}{[(1*E*)-2-(5-chloro-2-thienyl)-1-propen-1-yl]sulfonyl}amino)-2-oxo-1-pyrrolidinyl]-3-fluoro-*N*,*N*-dimethylbenzamide;
4-{(3*S*)-3-[{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}(cyclopentyl)amino]-2-oxo-1-pyrrolidinyl}-3-fluoro-*N*,*N*-dimethylbenzamide;
4-((3*S*)-3-{{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}[(1-methyl-1H-imidazol-2-yl)methyl]amino}-2-oxo-1-pyrrolidinyl)-3-fluoro-*N*,*N*-dimethylbenzamide;
4-{(3*S*)-3-[{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}(1-methylethyl)amino]-2-oxo-1-pyrrolidinyl}-3-fluoro-*N*,*N*-dimethylbenzamide;
4-{(3*S*)-3-[{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}(2-pyridinylmethyl)amino]-2-oxo-1-pyrrolidinyl}-3-fluoro-*N*,*N*-dimethylbenzamide;

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4-((3*S*)-3-{{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}[(3,5-dimethyl-4-isoxazolyl)methyl]amino}-2-oxo-1-pyrrolidinyl)-3-fluoro-*N*,*N*-dimethylbenzamide;
4-((3*S*)-3-{{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}[2-(methyloxy)ethyl]amino}-2-oxo-1-pyrrolidinyl)-3-fluoro-*N*,*N*-dimethylbenzamide;
4-[(3*S*)-3-({[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}{2-[(1,1-dimethylethyl)oxy]ethyl}amino)-2-oxo-1-pyrrolidinyl]-3-fluoro-*N*,*N*-dimethylbenzamide;
4-[(3*S*)-3-({(3-Amino-2-pyrazinyl)methyl}{[(1*E*)-2-(5-chloro-2-thienyl)-1-propen-1-yl]sulfonyl}amino)-2-oxo-1-pyrrolidinyl]-3-fluoro-*N*,*N*-dimethylbenzamide;
4-{(3*S*)-3-[{[(1*E*)-2-(5-Chloro-2-thienyl)-1-propen-1-yl]sulfonyl}(methyl)amino]-2-oxo-1-pyrrolidinyl}-3-fluoro-*N*,*N*-dimethylbenzamide;
4-{(3*S*)-3-[{[(*E*)-2-(5-chloro-2-thienyl)ethenyl]sulfonyl}(methyl)amino]-2-oxo-1-pyrrolidinyl}-3-fluoro-*N*,*N*-dimethylbenzamide;
and/or pharmaceutically acceptable derivative thereof.

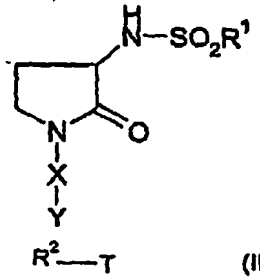
8. A compound according to any one of claims 1-7 and/or pharmaceutically acceptable derivative thereof for use in therapy.

9. A pharmaceutical composition comprising a compound according to any one of claims 1-7 and/or pharmaceutically acceptable derivative thereof together with at least one pharmaceutical carrier and/or excipient.

10. Use of a compound according to any one of claims 1-7 and/or pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.

11. A method of treating a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor comprising administering a therapeutically effective amount of a compound according to any one of claims 1-7 and/or pharmaceutically acceptable derivative thereof.

12. A process for preparing a compound of formula (I) which comprises reacting a compound of formula (II) with a compound of formula (III):



(II)

(III)

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